A multinational case-control study on childhood brain tumours, anthropogenic factors, birth characteristics and prenatal exposures: a validation of interview data

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Abstract

Little is known about the aetiology of childhood brain tumours. We investigated anthropometric factors (birth weight, length, maternal age), birth characteristics (e.g. vacuum extraction, preterm delivery, birth order) and exposures during pregnancy (e.g. maternal: smoking, working, dietary supplement intake) in relation to risk of brain tumour diagnosis among 7–19 year olds. The multinational case-control study in Denmark, Sweden, Norway and Switzerland (CEFALO) included interviews with 352 (participation rate=83.2%) eligible cases and 646 (71.1%) population-based controls. Interview data were complemented with data from birth registries and validated by assessing agreement (Cohen's Kappa). We used conditional logistic regression models matched on age, sex and geographical region (adjusted for maternal age and parental education) to explore associations between birth factors and childhood brain tumour risk. Agreement between interview and birth registry data ranged from moderate (Kappa=0.54; worked during pregnancy) to almost perfect (Kappa=0.98; birth weight). Neither anthropogenic factors nor birth characteristics were associated with childhood brain tumour risk. Maternal vitamin intake during pregnancy was indicative of a protective effect (OR 0.75, 95%-CI: 0.56-1.01). No association was seen for maternal smoking during pregnancy or working during pregnancy. We found little evidence that the considered birth factors were related to brain tumour risk among children and adolescents.

INTRODUCTION

Primary central nervous system (CNS) neoplasms, of which >90% are located in the brain, are the second most common malignancy and the most common solid cancer in children in developed countries.[1] While brain tumours during childhood often occur before the age of five, suggesting that both prenatal and early postnatal exposures must be considered, it remains one of the most common childhood cancers across the whole child-adolescent age spectrum.[2] The annual incidence rate of CNS tumours in children aged 0-14 years is 30 per million in Europe,[3] 35 per million in Switzerland[4] and 42 per million in the Nordic countries.[5]

Despite decades of epidemiological research, the aetiology of primary brain tumours in children and adolescents largely remains unknown.[6] Apart from ionizing radiation and a few genetic syndromes such as neurofibromatosis and tuberous sclerosis, no risk factors have been identified.[7] Many potential risk factors, however, have been studied including head injuries,[8] maternal and paternal smoking,[9, 10] maternal diet (especially cured meat),[11] maternal age and birth characteristics such as birth weight or birth order,[12, 13] atopy,[14] exposure to infectious agents,[15, 16] exposure to pesticides,[17] parental occupation,[18] maternal medication and vitamin intake during pregnancy[19, 20] and electromagnetic fields from mobile phones.[21] Most of these studies yielded inconclusive and conflicting results and often faced methodological limitations. The established risk factors collectively account for only 5% of all brain tumours in children[7] and a recent study estimated that the majority of cancer risk is due to random mutations due to cell division - only one third of the variance in cancer risk for tissues was attributable to environmental or inheritance factors.[22]

We investigated several anthropometric factors, birth characteristics and exposures during pregnancy in relation to brain tumour diagnosis among children and adolescents aged 7–19 using

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data from CEFALO, a multinational case-control study conducted in Denmark, Sweden, Norway and Switzerland. We validated the interview data with data from the birth registries to evaluate recall bias and exposure misclassification.

MATERIALS AND METHODS

Study population

Cases

Eligible cases were all children in Denmark, Sweden, Norway and Switzerland diagnosed between 2004 and 2008 with primary intracranial central nervous system tumours (CNS) aged 7 to 19 years at diagnosis.[21] Brain tumours were defined as per the International Classification of Diseases tenth revision (ICD-10) and International Classification of Diseases for Oncology third edition (ICD-O-3). All diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. We examined medical records for case patients to confirm diagnosis and establish the date of diagnosis (used as reference date in the exposure assessment). Date of diagnosis was defined as the date when the first diagnostic imaging was performed. Case patients were excluded if they were diagnosed with neurofibromatosis (Mb Recklinghausen; 12 patients) or tuberous sclerosis (1 patient). Since the initial hypothesis of CEFALO was on the use of mobile phones, participants who were completely deaf prior to the reference date and children with severe mental retardation were excluded (2 patients and 2 control subjects). Families with insufficient language skills to complete an interview in the respective country, as judged by a nurse, treating physician, or project administrator, were excluded (15 patients and 36 control subjects).

Controls

We randomly selected two control subjects per case patient using population registries in the participating countries, individually matched by age (Denmark, Sweden, and Switzerland: by year and month of birth; Norway: by year of birth), sex, country, and geographical region within country. In Switzerland, a two-stage random sampling procedure was applied in the absence of a national population registry. A community was randomly determined within the same language region as each patient, next the control subject was randomly selected from the corresponding communal population registry. The reference date for control subjects was same as the date of diagnosis of the matched case patient.

Data collection

Children were accompanied by at least one parent (preferably the mother) and were interviewed face-to-face by trained interviewers using a computer-assisted personal interview (CAPI) questionnaire (Denmark and Norway) or a paper version of the questionnaire (Switzerland and Sweden). In exceptional circumstances, telephone interviews were conducted with difficult-to-reach participants (4 control subjects) or an adapted paper version of the questionnaire was sent (19 control subjects). Interviews with case patients and matched control subjects were mainly performed by the same interviewer. Interviewers from all centres received training at a joint workshop to ensure uniform data collection. Questionnaire translations were checked through back-translation to the master version (English), and the questionnaires were pilot-tested in all participating countries.

All case patients were interviewed within 5 years of diagnosis (63% within 2 years). The accompanying parent responded to questions related to pregnancy and early life exposures.

Exposure information

Interview questions were aimed at collecting both infant as well as parental characteristics. Anthropometric factors were birth weight, birth length, and age of the mother (<25, 25–34, ≥35 years). Birth characteristics were Caesarean section (yes, no), vacuum extraction (yes, no), use of obstetrical forceps (yes, no), if the child was born premature (i.e. ≥3 weeks early; yes, no), birth order of the child in the family (1st born, later born), and if the mother ever had a miscarriage or a stillbirth (yes, no). We considered the following variables as exposures: maternal smoking during pregnancy (yes, no), maternal vitamin intake during pregnancy (yes, no), maternal intake of vitamins with folic acid (yes, no), working during pregnancy (yes, no), hours worked during pregnancy (full-time, part-time, not worked), shift work during pregnancy (yes, no), and maternal diabetes during pregnancy (yes, no).

In addition to the CEFALO questionnaire, supplementary data from national birth registries in Sweden, Denmark and Norway were obtained. Registry data were not available for Switzerland. For anthropometric factors we obtained birth weight, birth length, head circumference and gestational age in weeks. Birth characteristics comprised Caesarean section (yes, no), vacuum extraction (yes, no), use of obstetrical forceps (yes, no), ever stillbirth or miscarriage (yes, no), single or multiple births (singleton, multiple birth) and parity (first born, not first born). Specific exposures during pregnancy related to maternal smoking at first visit to maternity clinic (yes, no), working during pregnancy (yes, no) and hours worked during pregnancy (full-time, part-time, not worked).

Statistical analysis

Agreement between interview data and data from the birth registries was calculated by Cohen's Kappa.[23] Weighted Kappa was used for variables with more than two categories. We considered

agreement to be moderate if the Kappa value was 0.4-0.6, substantial for 0.6-0.8, and almost perfect >0.8.

Odds ratios (ORs) and 95%-confidence intervals (95%-CIs) to estimate the strength and precision of association between the possible risk factors and brain tumour risk were based on conditional logistic regression models matched on age, sex, and geographical region. We additionally adjusted for maternal age and parental education. To gap fill missing confounder information: we applied the most common category for parental education (n=3); and for maternal age (n=11) we imputed missing values based on age of the child, paternal age, country and region. All statistical tests were two-sided. For categorical variables, test for trends were calculated by assigning ordered exposure levels (e.g., 1, 2, 3). We assessed the risk for all histologic types of brain tumours combined, and specifically for astrocytoma, where numbers were large enough to allow a subgroup analysis.

The software Stata/SE version 13.0 (StataCorp, Texas, USA) was used for all analyses.

RESULTS

In total, 423 patients and 909 potential controls were identified during the CEFALO study period. Interviews were completed with 352 (83.2%) eligible cases and 646 (71.1%) eligible controls (Table 1). Among the 352 case patients of CNS cancer, astrocytoma was the most common type with 162 (46.0%) cases (Table 1). There were 21 (6.0%) cases diagnosed with ependymoma, 30 (8.5%) with another glioma, 62 (17.6%) with primitive neuroectodermal tumours, 53 (15.1%) with other specified intracranial neoplasms and 24 (6.8%) with unspecified intracranial neoplasms.

The agreement between data reported in the interview and data collected from the birth registries ranged from moderate (Kappa=0.54 for worked and hours worked during pregnancy) to almost perfect (Caesarean section, birth weight and whether or not the child was a singleton; Table 2). Although some Kappa coefficients were marginally higher in cases, there was no evidence of a systematic difference between cases and controls.

Results for the association between reported anthropometric factors, birth characteristics and exposures during pregnancy and the risk of all brain tumours among children and adolescents are shown in Table 3; Table S1 (online supplement) shows results for the analysis restricted to astrocytoma cases. We found no evidence for an increased risk of brain tumours for any of the anthropometric factors. Children with a brain tumour were not more likely to have had a birth weight ≥4000g compared to controls. Birth characteristics, such as intervention during birth or prematurity, did not alter the risk of being diagnosed with a brain tumour. Odds ratios seemed to fluctuate around unity and no clear tendency was seen for any of the considered birth characteristics.

Maternal vitamin intake during pregnancy was indicative, though not statistically significant, of a protective effect for childhood brain tumours (adjusted OR 0.75, 95%-CI: 0.56-1.01; Table 3). No association, however, was observed in the subset of mothers who indicated that their vitamin supplements contained folic acid (Table 1), or in patients with astrocytoma (Table S1). All other considered exposures, such as work during pregnancy and maternal diabetes (i.e. existing maternal diabetes or maternal gestational diabetes), indicated no increased risk. Analyses restricted to astrocytoma (Table S1) gave broadly similar results compared to the full sample.

Table 4 reports the associations based on data collected in the birth registries, and compares the estimates with interview based exposure data for the same study sample (without Switzerland).

We found no evidence for an increased risk of brain tumours for any of the measures evaluated in the birth registries. Risk estimates were similar for birth registry and interview data for all variables except smoking where risk estimates slightly above unity were observed for interview data vs. close to unity for the registry data. The 95%-confidence intervals, however, were overlapping to a large extent. Regarding risk of astrocytoma, we saw evidence of a protective effect of working during pregnancy (adjusted OR 0.14, 95%-CI: 0.02-0.97) and specifically for part-time work during pregnancy (adjusted OR 0.09, 95%-CI: 0.01-0.97), though only in a small sample with interview data (Table S2).

DISCUSSION

The relationship between pre- and postnatal characteristics and exposures and the risk of childhood brain tumours has been investigated in many studies, often with inconclusive results.[12, 24-29] A birth weight ≥4000g has been repeatedly associated with an increased risk for childhood brain tumours and other cancers.[28, 30] In a meta-analysis by Harder, et al. [31] including 1.7 mil children and ~4000 cases, the odds ratios for the relationship between high birth weight and childhood brain tumours were 1.38 (95%-CI: 1.07-1.79) and 1.27 (95%-CI: 1.02-1.60), respectively for medulloblastoma and astrocytoma. We observed no such association in our study population for astrocytoma risk and birth weight from interview or registry data (Table S1 and S2). Our sample of children with a birth weight ≥4000g, however, was relatively small and the statistical power to detect an association was limited. Furthermore, since the primary aim of CEFALO was to address the risk from mobile phone use,[21] our age range of 7-19 years was different to that of most other studies, usually focussed on 0-14 year olds, and the association with prenatal factors may be stronger in the youngest children as shown in Schmidt, et al. [28] In

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addition, we found no indication that birth length, head circumference or maternal age at birth alters the risk of childhood brain tumours.

We found a tendency that children whose mother reported to have smoked during pregnancy had a higher risk of brain tumours compared to children of non-smoking mothers (Table 3). This tendency, however, was not apparent when we looked at the association using registry-recorded smoking status (Table 4). The relationship between maternal smoking and childhood brain tumour risk has been reported by a few studies[10, 32] but most found no evidence for an association.[9, 24, 29, 33, 34, 35] A meta-analysis found an overall risk estimate of 1.05 (95%-CI: 0.90-1.21).[36] Most of these studies were case-control studies that assessed the exposure retrospectively raising the question of recall bias. Recall bias could potentially be in both directions. Case mothers may over-report their smoking during pregnancy because they consider smoking a relevant risk factor to report. Or they may under-report because they do not want to be accused of having done harm to their child. A particular strength of our study is that we used prospectively collected smoking data, from the birth registry, which cannot suffer from recall bias. We found similar agreement between interview and registry data for cases and controls (Table 2), although the false positive rate was slightly higher in cases (8%) than in controls (4%) producing a slightly elevated odds ratio of smoking for interview compared to registry data.

The observed indication for a protective effect of maternal vitamin supplements during pregnancy is in line with other investigations,[19, 37] although recall bias is a concern for all these case-control studies using retrospectively collected exposure data (Table 3). This may also be of concern in our study, because we had no such data available from the birth registry. Another explanation for the observed effect is confounding. Vitamin intake during pregnancy may indicate a healthier lifestyle in general. We did not observe an association for maternal intake of vitamin supplements

that contained folic acid.[38] Non-differential exposure misclassification, however, is a plausible explanation since it can be assumed that the mothers were often not aware that the vitamin supplements they took contained folic acid. So far, the exact constituents among the multivitamins that could confer a protective effect are unknown.[19]

Night shift work was proposed as a risk factor for breast and endometrial cancer,[39, 40] and is classified as a probable carcinogen (class 2A) by the International Agency for Research on Cancer's programme on the evaluation of carcinogenic risks to humans.[41] Although we did not have a large enough sample to specifically explore shift work at night, we did not see an increased risk of any brain tumours for offspring of mothers who reported any shift work (day or night) during pregnancy (Table 3). We saw a possible protective association between working, and specifically part-time work, during pregnancy and astrocytoma (Table S2) indicating a potential "healthy worker" effect.[42] This result, however, was not robust. The association was found with interview data but disappeared when exposure was assigned using the birth registry data. Furthermore, no association was found in the full astrocytoma subset after adjustment for confounders (Table S1).

Strengths and limitations

In addition to the data obtained through the CEFALO questionnaire, a unique feature of our analysis is that we used birth registry data to explore the association between exposures during pregnancy and risk of childhood brain tumours, notably recorded before the diagnosis of the disease. This was possible in three of the four countries. In the Nordic Countries notification to the medical birth registers is mandatory and, for a large part of our study period, also automated. All Nordic medical birth registers are considered to be virtually complete.[43] Even if birth registry data is sometimes also self-reported and subject to error and censoring (e.g. smoking status

during pregnancy), data are collected prospectively, thus error cannot be related to health status and is expected to be non-differential. Retrospectively collected interview data, on the other hand, may result in an overestimation of the risk if cases overestimate their exposure, or in an underestimation if cases under-report exposures.

Interestingly, we noted often very slightly higher concordance for the cases than controls, which may indicate some differential exposure misclassification is at play. Since this pattern was mostly seen in the very high Kappa range (>0.8), it may also simply indicate that a small proportion of control mothers are perhaps less careful or thorough in answering the questionnaire. Either way, it indicates the potential for differential exposure misclassification, which might produce biased risk estimates.

Using the international population-based CEFALO study and two independent sources of exposure data, we found no consistent associations between a variety of anthropometric factors, birth characteristics and exposures during pregnancy and risk of brain tumours among children and adolescents. Our comparison of the two sources of exposure data, however, indicates some potential for differential exposure misclassification and thus potentially biased risk estimates when relying on interview data alone. It is, therefore, reassuring that analyses of factors for which birth registry data were available were consistent with the analyses using interview data.

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Table 1. Characteristics of the study participants

Characteristic	Full sample Cases (n=352) No. (%)	Controls (n=646) No. (%)	Astrocytoma subset Cases (n=162) No. (%)	Controls (n=295) No. (%)
Country				
Denmark	85 (24.1)	170 (26.3)	41 (25.3)	82 (27.8)
Sweden	138 (39.2)	228 (35.3)	55 (34.0)	89 (30.2)
Norway	44 (12.5)	78 (12.1)	23 (14.2)	38 (12.9)
Switzerland	85 (24.2)	170 (26.3)	43 (26.5)	86 (29.1)
Age at reference date, years				
7-9	88 (25.0)	167 (25.9)	35 (21.6)	65 (22.0)
10-12	82 (23.3)	151 (23.4)	46 (28.4)	83 (28.1)
13-15	99 (28.1)	183 (28.3)	43 (26.5)	79 (26.8)
16-19	83 (23.6)	145 (22.5)	38 (23.5)	68 (23.1)
Sex				
Female	162 (46.0)	293 (45.4)	86 (53.1)	161 (54.6)
Male	190 (54.0)	353 (54.6)	76 (46.9)	134 (45.4)
Gestational age, weeks [a]				
missing data	118 (33.5)	206 (31.9)	52 (32.1)	104 (35.2)
<32	1 (0.3)	4 (0.6)	0 (0)	4 (1.4)
32 - 37	9 (2.6)	14 (2.2)	4 (2.5)	7 (2.4)
≥37	224 (63.6)	422 (65.3)	106 (65.4)	180 (61.0)
Educational level [b]				
Low	20 (5.7)	26 (4.0)	12 (7.4)	10 (3.4)
Intermediate	188 (53.4)	336 (52.0)	85 (52.5)	156 (52.9)
High	144 (40.9)	279 (43.2)	65 (40.1)	128 (43.4)
Unknown	0 (0)	5 (0.8)	0 (0)	1 (0.3)

Notes:

a. Based on registry data, all other variables based on interview data

b. Based on highest attained level of either parent. High = graduating from university or technical college; Intermediate = elementary school, diploma school, or apprenticeship; and Low = elementary school not completed

Table 2. Agreement between interview data and birth registry data (Cohen's Kappa)

Variable [a]	Registry Data	No. Overall	Kappa overall	No. Cases	Kappa cases	No. Controls	Kappa controls
Birth weight [b]	SE, DK, NO	680	0.98	242	0.99	438	0.98
Birth length [c]	SE, DK, NO	668	0.92	238	0.95	430	0.91
Caesarean section	SE, DK, NO	352	0.95	135	1.00	217	0.91
Vacuum extraction	SE, DK, NO	464	0.72	169	0.72	295	0.72
Forceps	SE, DK, NO	454	0.85	165	0.89	289	0.83
Smoking during pregnancy [d]	SE, NO	315	0.77	122	0.75	193	0.79
Work during pregnancy	SE	264	0.54	97	0.61	167	0.50
Hours worked during pregnancy [e]	SE	262	0.54	97	0.53	165	0.55
Ever stillbirth/miscarriage	SE, DK, NO	252	0.71	85	0.71	167	0.71
Single or multiple births	SE, DK	574	0.96	203	1.00	371	0.94

Notes:
a. Weighted kappa was used for ordinal categories: birth weight, birth length, and hours worked during pregnancy. All other variables were binary.
b. Birth weight categories based on definition of low (<2500g) and high (≥4000g) birth weight
c. Birth length categories defined based on 25th and 75th percentile of birth length for the control subjects
d. Binary response to interview question "did you smoke during pregnancy?" vs. Registry question "smoking at first visit to maternity clinic."
e. Hours worked during pregnancy (full time, part time, not worked)

Table 3. Relationship between exposures and brain tumour risk among children and adolescents based on interview data

Variable	Cases No.	Controls No.	OR (95%-CI) [a] Unadjusted	OR (95%-CI) [a] Adjusted [b]
Anthropometric factors:				
Birth weight [c]				
<2500 g	20	25	1.45 (0.79-2.66)	1.53 (0.83-2.82)
2500-4000 g	274	508	1.0	1.0
≥ 4000 g	53	95	1.06 (0.73-1.54)	1.09 (0.74-1.58)
p value for trend				*0.581*
Birth length [d]				
≤ 49 cm	104	180	1.05 (0.76-1.44)	1.03 (0.75-1.42)
50-52 cm	163	295	1.0	1.0
≥ 53 cm	67	122	1.04 (0.72-1.49)	1.04 (0.72-1.49)
p value for trend				*0.744*
Age of the mother				
<25 years	80	120	1.0	1.0
25-29	131	249	0.81 (0.56-1.16)	0.82 (0.57-1.19)
30-34	97	181	0.82 (0.56-1.22)	0.85 (0.57-1.26)
≥ 35	41	85	0.73 (0.46-1.16)	0.74 (0.46-1.18)
p value for trend				*0.158*
Birth characteristics:				
Caesarean section				
No	300	541	1.0	1.0
Yes	47	86	0.98 (0.66-1.45)	0.99 (0.67-1.48)
Vacuum extraction				
No	304	541	1.0	1.0
Yes	40	74	0.99 (0.64-1.52)	0.98 (0.63-1.51)
Forceps				
No	334	599	1.0	1.0
Yes	10	16	1.13 (0.49-2.64)	1.11 (0.47-2.61)
Born premature (at least 3 weeks too early)				
No	318	558	1.0	1.0
Yes	26	52	0.86 (0.53-1.40)	0.85 (0.52-1.39)
Ever stillbirth/miscarriage				
No	239	413	1.0	1.0
Yes	104	196	0.92 (0.69-1.22)	0.92 (0.69-1.23)
Birth order				
1st born	148	254	1.0	1.0
≥2nd born	203	385	0.87 (0.67-1.14)	0.90 (0.68-1.20)
Single or multiple births				
Singleton	342	622	1.0	1.0
Multiple birth	8	15	1.00 (0.41-2.41)	1.04 (0.43-2.53)

Variable	Cases No.	Controls No.	OR (95%-CI) [a] Unadjusted	OR (95%-CI) [a] Adjusted [b]
Exposures:				
Maternal smoking during pregnancy				
No	258	493	1.0	1.0
Yes	90	133	1.27 (0.94-1.73)	1.23 (0.90-1.68)
Maternal vitamin intake during pregnancy				
No	189	290	1.0	1.0
Yes	139	289	0.75 (0.56-1.01)	0.75 (0.56-1.01)
Maternal vitamin and folic acid intake during pregnancy				
No	230	380	1.0	1.0
Yes	59	93	1.10 (0.75-1.61)	1.15 (0.78-1.70)
Work during pregnancy				
No	99	154	1.0	1.0
Yes	248	471	0.80 (0.59-1.08)	0.82 (0.61-1.12)
Hours worked during pregnancy				
Not worked	99	154	1.0	1.0
Part-time (<40 hours/week)	165	313	0.80 (0.58-1.11)	0.84 (0.60-1.17)
Full time (40 hours/week)	81	149	0.81 (0.55-1.19)	0.83 (0.57-1.23)
p value for trend				_0.255_
Shift work during pregnancy				
Not worked or not shift worked	287	520	1.0	1.0
Shift worked	59	102	1.00 (0.69-1.45)	0.99 (0.68-1.44)
Maternal diabetes [e]				
No	341	610	1.0	1.0
Yes	6	14	0.76 (0.29-2.00)	0.76 (0.29-2.02)

Notes:

a. Conditional logistic regression models, matched on sex, age-group and geographical region

b. Adjusted for maternal age and parental education

c. Birth weight categories based on definition of low (<2500g) and high (≥4000g) birth weight

d. Birth length categories defined based on 25th and 75th percentile of birth length for the control subjects

e. Defined as existing maternal diabetes or maternal gestational diabetes

Table 4. Comparison of brain tumour risk among children and adolescents based on interview vs. birth registry data, based on the study population where both types of data are available

Variable	Interview data			Birth Registry data			Registry Data
	Cases No.	Controls No.	OR (95%-CI) [a] Adjusted [b]	Cases No.	Controls No.	OR (95%-CI) [a] Adjusted [b]	
Anthropometric factors:							
Birth weight [c]							SE, DK, NO
<2500 g	12	13	1.66 (0.72-3.86)	11	14	1.42 (0.63-3.21)	
2500-4000 g	177	313	1.0	178	313	1.0	
≥ 4000 g	47	71	1.31 (0.85-2.01)	47	70	1.33 (0.86-2.05)	
p value for trend			*0.743*			*0.488*	
Birth length [d]							SE, DK, NO
≤ 49 cm	58	93	0.96 (0.62-1.48)	59	94	0.96 (0.62-1.48)	
50-52 cm	120	194	1.0	121	193	1.0	
≥ 53 cm	54	97	0.98 (0.64-1.50)	52	97	0.91 (0.59-1.41)	
p value for trend			*0.641*			*0.565*	
Head circumference [e]							SE, DK, NO
< 38 cm	-	-	-	157	246	1.0	
≥ 38 cm	-	-	-	6	10	1.08 (0.37-3.15)	
Gestational age (per week) [e]	-	-	-	227	383	1.00 (0.91-1.08)	SE, DK, NO
Birth characteristics:							
Caesarean section							SE, DK, NO
No	103	159	1.0	103	161	1.0	
Yes	19	26	0.88 (0.44-1.78)	19	24	0.96 (0.47-1.97)	
Vacuum extraction							SE, DK, NO
No	141	235	1.0	150	241	1.0	
Yes	17	23	1.09 (0.53-2.23)	8	17	0.66 (0.25-1.74)	
No	154	252	1.0	155	254	1.0	
Yes	3	5	0.93 (0.21-4.10)	2	3	1.28 (0.20-8.10)	
Ever stillbirth/miscarriage							SE, DK, NO
No	45	83	1.0	55	102	1.0	
Yes	24	44	0.91 (0.46-1.80)	14	25	0.94 (0.38-2.33)	
Single or multiple births							
Singleton	194	327	1.0	194	328	1.0	SE, DK
Multiple birth	4	9	0.84 (0.24-2.94)	4	8	0.92 (0.26-3.34)	
Parity [e,f]							DK, NO
first birth	-	-	-	20	28	1.0	
not first birth	-	-	-	33	67	0.75 (0.33-1.71)	
Exposures:							
Maternal smoking during pregnancy							SE, NO
No	85	129	1.0	90	127	1.0	
Yes	29	37	1.25 (0.68-2.26)	24	39	0.96 (0.53-1.75)	

Variable	Interview data			Birth Registry data			Registry Data
	Cases	Controls	OR (95%-CI) [a]	Cases	Controls	OR (95%-CI) [a]	
	No.	No.	Adjusted [b]	No.	No.	Adjusted [b]	
Work during pregnancy							SE
No	14	19	1.0	11	14	1.0	
Yes	69	92	0.76 (0.31-1.86)	72	97	0.77 (0.30-1.95)	
Hours worked during pregnancy							SE
Not worked	14	19	1.0	11	14	1.0	
Part-time (<40 hours/week)	38	41	0.92 (0.35-2.42)	30	40	0.77 (0.29-2.06)	
Full time (40 hours/week)	31	50	0.68 (0.27-1.73)	42	56	0.78 (0.29-2.08)	
p value for trend			*0.160*			*0.292*	

Notes:

a. Conditional logistic regression models, matched on sex, age-group and geographical region

b. Adjusted for maternal age and parental education

c. Birth weight categories based on definition of low (<2500g) and high birth weight (>= 4000g)

d. Birth length categories defined based on 25th and 75th percentile of birth length for the control subjects

e. Head circumference, gestational age and parity were not inquired in the interview

f. Parity adjusted for maternal age only

Supplemental Information:

A multinational case-control study on childhood brain tumours, anthropogenic factors, birth characteristics and prenatal exposures: a validation of interview data

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Table S1. Relationship between exposures and astrocytoma risk among children and adolescents based on interview data

Variable	Cases No.	Controls No.	OR (95%-CI) [a] Unadjusted	OR (95%-CI) [a] Adjusted [b]
Anthropometric factors:				
Birth weight [c]				
<2500 g	9	18	0.81 (0.35-1.90)	0.84 (0.35-1.99)
2500-4000 g	129	222	1.0	1.0
≥ 4000 g	22	46	0.84 (0.48-1.47)	0.90 (0.51-1.59)
p value for trend				*0.711*
Birth length [d]				
≤ 49 cm	54	84	1.16 (0.74-1.80)	1.10 (0.70-1.74)
50-52 cm	71	135	1.0	1.0
≥ 53 cm	30	53	1.06 (0.62-1.80)	1.05 (0.61-1.80)
p value for trend				*0.640*
Age of the mother				
<25 years	33	47	1.0	1.0
25-29	62	120	0.75 (0.42-1.31)	0.85 (0.47-1.51)
30-34	45	83	0.83 (0.45-1.51)	0.93 (0.50-1.72)
≥ 35	20	39	0.72 (0.36-1.45)	0.77 (0.38-1.57)
p value for trend				*0.380*
Birth characteristics:				
Caesarean section				
No	132	245	1.0	1.0
Yes	28	40	1.26 (0.73-2.15)	1.28 (0.74-2.23)
Vacuum extraction				
No	138	243	1.0	1.0
Yes	19	33	1.05 (0.56-1.97)	1.08 (0.57-2.03)
Forceps				
No	150	267	1.0	1.0
Yes	7	9	1.54 (0.51-4.62)	1.43 (0.47-4.39)
Born premature (at least 3 weeks too early)				
No	147	251	1.0	1.0
Yes	12	26	0.77 (0.38-1.54)	0.78 (0.38-1.58)
Ever stillbirth/miscarriage				
No	110	193	1.0	1.0
Yes	48	83	1.02 (0.67-1.57)	1.01 (0.65-1.56)
Birth order				
1st born	71	125	1.0	1.0
≥2nd born	91	167	0.96 (0.65-1.41)	0.97 (0.64-1.47)
Single or multiple births				
Singleton	158	282	1.0	1.0
Multiple birth	4	10	0.74 (0.22-2.47)	0.84 (0.25-2.88)

Variable	Cases No.	Controls No.	OR (95%-CI) [a] Unadjusted	OR (95%-CI) [a] Adjusted [b]
Exposures:				
Maternal smoking during pregnancy				
No	120	227	1.0	1.0
Yes	41	58	1.34 (0.84-2.13)	1.26 (0.78-2.04)
Maternal vitamin intake during pregnancy				
No	83	132	1.0	1.0
Yes	65	129	0.81 (0.52-1.27)	0.76 (0.48-1.20)
Maternal vitamin and folic acid intake during pregnancy				
No	105	178	1.0	1.0
Yes	29	38	1.34 (0.75-2.40)	1.41 (0.77-2.58)
Work during pregnancy				
No	56	78	1.0	1.0
Yes	104	206	0.65 (0.42-1.01)	0.70 (0.45-1.09)
Hours worked during pregnancy				
Not worked	56	78	1.0	1.0
Part-time (<40 hours/week)	74	143	0.67 (0.41-1.08)	0.75 (0.46-1.24)
Full time (40 hours/week)	29	59	0.66 (0.38-1.17)	0.70 (0.39-1.24)
p value for trend				*0.130*
Shift work during pregnancy				
Not worked or not shift worked	146	242	1.0	1.0
Shift worked	14	42	0.50 (0.26-0.95)	0.52 (0.27-1.01)
Maternal diabetes [e]				
No	155	279	1.0	1.0
Yes	5	4	2.33 (0.62-8.72)	2.80 (0.72-10.93)

Notes:

a. Conditional logistic regression models, matched on sex, age-group and geographical region

b. Adjusted for maternal age and parental education

c. Birth weight categories based on definition of low (<2500g) and high (≥4000g) birth weight

d. Birth length categories defined based on 25th and 75th percentile of birth length for the control subjects

e. Defined as existing maternal diabetes or maternal gestational diabetes

Table S2. Comparison of astrocytoma risk among children and adolescents based on interview vs. birth registry data based on the study population, where both types of data are available

Variable	Interview data			Birth Registry data			Registry Data
	Cases No.	Controls No.	OR (95%-CI) [a] Adjusted [b]	Cases No.	Controls No.	OR (95%-CI) [a] Adjusted [b]	
Anthropometric factors:							
Birth weight [c]							SE, DK, NO
<2500 g	5	10	0.70 (0.21-2.37)	4	11	0.57 (0.17-1.86)	
2500-4000 g	83	137	1.0	84	137	1.0	
≥ 4000 g	19	32	1.18 (0.60-2.34)	19	31	1.20 (0.60-2.42)	
p value for trend			*0.894*			*0.629*	
Birth length [d]							SE, DK, NO
≤ 49 cm	29	45	0.84 (0.43-1.64)	31	45	0.99 (0.51-1.93)	
50-52 cm	51	82	1.0	49	83	1.0	
≥ 53 cm	24	41	0.98 (0.52-1.86)	24	40	1.07 (0.56-2.06)	
p value for trend			*0.544*			*0.477*	
Head circumference [e]							SE, DK, NO
< 38 cm	-	-	-	71	109	1.0	
≥ 38 cm	-	-	-	3	6	1.03 (0.24-4.42)	
Gestational age (per week)	-	-	-	106	179	1.02 (0.91-1.15)	SE, DK, NO
Birth characteristics:							
Caesarean section	40	65	1.0	40	65	1.0	SE, DK, NO
No	12	13	1.24 (0.40-3.82)	12	13	1.24 (0.40-3.82)	
Yes							
Vacuum extraction	57	98	1.0	61	100	1.0	SE, DK, NO
No	8	9	1.13 (0.34-3.75)	4	7	0.84 (0.19-3.68)	
Yes							
No	64	104	1.0	64	105	1.0	
Yes	1	3	0.53 (0.05-5.36)	1	2	0.98 (0.08-11.55)	
Ever stillbirth/miscarriage							SE, DK, NO
No	24	41	1.0	26	48	1.0	
Yes	8	18	0.71 (0.23-2.19)	6	11	0.83 (0.22-3.13)	
Single or multiple births							
Singleton	85	146	1.0	85	146	1.0	SE, DK
Multiple birth	3	5	1.03 (0.21-5.13)	3	5	1.03 (0.21-5.13)	
Parity [e,f]							DK, NO
first birth	-	-	-	12	16	1.0	
not first birth	-	-	-	17	33	0.73 (0.22-2.41)	
Exposures:							
Maternal smoking during pregnancy							SE, NO
No	34	51	1.0	37	49	1.0	
Yes	13	17	0.97 (0.35-2.68)	10	19	0.59 (0.22-1.58)	
Work during pregnancy							SE
No	9	5	1.0	7	1	1.0	
Yes	22	35	0.14 (0.02-0.97)	24	39	0.14 (0.01-1.29)	

	Interview data			Birth Registry data			Registry Data
Variable	Cases	Controls	OR (95%-CI) [a]	Cases	Controls	OR (95%-CI) [a]	
	No.	No.	Adjusted [b]	No.	No.	Adjusted [b]	
Hours worked during pregnancy							SE
Not worked	9	5	1.0	7	1	1.0	
Part-time (<40 hours/week)	11	18	0.09 (0.01-0.97)	9	17	0.13 (0.01-1.29)	
Full time (40 hours/week)	11	17	0.15 (0.02-1.06)	15	22	0.15 (0.01-1.43)	
p value for trend			*0.073*			*0.035*	

Notes:

a. Conditional logistic regression models, matched on sex, age-group and geographical region

b. Adjusted for maternal age and parental education

c. Birth weight categories based on definition of low (<2500g) and high birth weight (>= 4000g)

d. Birth length categories defined based on 25th and 75th percentile of birth length for the control subjects

e. Head circumference and parity were not inquired in the interview

f. Parity adjusted for maternal age only